REMARKS

After amendment, the pending claims are 81 and 103-107. Claims 10-13, 39, 67, 83, 100 and 102 are canceled and Applicant reserves the right to prosecute the invention of these claims and any deleted subject matter in a divisional filed during the pendency of the present application. New claims 103-107 are supported by the original specification and claims.

The specification and claims were amended to clarify the invention and place the application in condition for allowance. No new matter is added by these amendments. Support for the amendments is found in the original specification and claims as filed. See, particularly, page 11, lines 1-2 and 20; page 15, lines 14-16; page 16, lines 4-8; page 17, lines 24-28; pages 26-30; and elsewhere throughout the specification.

Applicant has enclosed as Appendix A, a version of the amended claims with markings to show changes made; material added is indicated by highlighting and material deleted is indicated by bolded bracketing. Applicant has also enclosed as Appendix B, a clean copy of the pending claims.

Specification Objections

The Examiner has objected to the specification for the following reasons and has indicated that:

(a) The ATCC numbers are blank on page 10, lines 13-14.

Applicant respectfully requests reconsideration and withdrawal of this objection for the following reason. In an effort to place the application in condition for allowance, Applicant has amended page 10 by inserting the omitted ATCC numbers.

Reconsideration of this objection is requested.

(b) If a deposit has been made under the provisions of the Budapest Treaty an Affidavit or Declaration must be filed asserting that all restrictions will be removed upon grant to a patent on this application.

Applicant respectfully requests reconsideration and withdrawal of this objection for the following reason. In an effort to place the application in condition for allowance, Applicant has forwarded herewith a Declaration of Biological Culture Deposit and Certification under 37 CFR § 3.73 executed by an individual authorized to sign on behalf of the Assignee.

Reconsideration of this objection is requested.

(c) The specification must be amended to recite the date of deposit and the name and street address of the depository.

Applicant respectfully requests reconsideration and withdrawal of this objection for the following reason. In an effort to place the application in condition for allowance, Applicant has amended page 10 by updating the street address of the depository. The dates of deposit were properly noted in the specification at the time of filing.

Reconsideration of this objection is requested.

35 USC 112, First Paragraph Rejections

The Examiner rejected claims 10-13, 81, and 100 under 35 USC § 112, first paragraph for the following reasons.

(a) The Examiner rejected claims 10-13 and asserted that there is no designation of the source of the protein, i.e., bacteria, yeast, genus, species, strain, etc.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. New independent claim 103 recites the specific SEQ ID NOs identifying the recombinant or synthetic protein or peptide. No designation of source is necessary to provide further definiteness to these claims.

Reconsideration of this rejection is requested.

(b) The Examiner has rejected claims 81 and 100 and has asserted that the specification does not reasonably enable detection using other fragments, homologs, analogs, or fusion proteins of P39.5 or P7-1.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. Claim 100 is canceled. Claim 103 recites that fragments of the specified sequences may be used that react with antibody from infected humans or animals. See, for support, specification page 15, lines 14-16; page 42, lines 24-30 and Examples 6 and 7. Ther terms "homologs, analogs and fusion proteins" have been eliminated from the claims.

Peptide fragments of the invention are represented by SEQ ID NOS: 2, 14 and encoded by SEQ ID NOS: 3, 7, and 11, as claimed in the specification. These peptides are capable of reacting with antisera from monkeys infected with the *Borrelia* strains that cause Lyme Disease, as disclosed in the specification. Specifically, the specification refers to a number of sequences of SEQ ID NO: 1, such as that encoded by bp 1-309 (page 7, line 15), bp 627-712 (page 11, lines 1-2), bp 769-854 (page 7, line 14), and bp 793-816 (page 11, line 24). Other small fragments of about 8 amino acids in length are disclosed on page 11, and including the P1-1 fragment, which duplicates nucleotides 683-960 of SEQ ID NO: 1 and were noted to react with antibodies from infected monkeys (specification page 15, lines 14-16).

Further support for the assertions in the specification as to the usefulness of such peptides and fragments may be found in the attached Rule 132 Declaration. This Declaration provides data from subsequent studies conducted by the inventor, which support the disclosures in this specification as to the activity of the sequences and fragments of the sequences recited in the present specification.

Clearly both the specification and subsequent additional work performed by Applicant supports that protein or peptide fragments represented by SEQ ID NOS: 1 and 2, and 13 and 14, and peptides encoded by SEQ ID NOS: 3, 7 and 11 are useful in the present invention. Note that the sequences of SEQ ID NOS: 3, 7 and 11 contain sequences encoding overlapping peptide sequences from SEQ ID NOS: 1 and 2.

Applicant submits that the usefulness of fragments of the peptides disclosed in the specification in reacting with antibody in animals with Lyme Disease is

amply supported by the specification and that the assertions of the specification with respect to such fragments is again supported by later work indicated in the Declaration.

In view of this evidence and these remarks, reconsideration and withdrawal of this rejection is requested.

(c) The Examiner has rejected claim 39 and has asserted that the phrase "a *Borrelia*" encompasses all of the *Borrelia* genus.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. Claim 39 is canceled and new claim 103 specifically identifies the peptides and proteins by their specific sequences.

Reconsideration of this rejection is requested.

35 USC § 112, Second Paragraph Rejections

The Examiner rejected claims 10-13, 81, and 100 under 35 USC § 112, second paragraph for the following reasons.

(a) The Examiner rejected claims 10-13 under 35 USC § 112, second paragraph and asserted that there is insufficient antecedent basis for the term "the P39.5 protein".

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. Claims 10-13 and 100 are cancelled; amended claim 81 and new claims 103-104 do not use the term "the P39.5 protein".

Reconsideration and withdrawal of this rejection is requested.

(b) The Examiner rejected claims 81 and 83 and asserted that the terms "analog", "homologs" and "fusion proteins" are unclear.

The Examiner further asserted that embodiments (d), (j), and (k) are indefinite for both structure and function.

The Examiner also asserted that it is unclear how the protein of embodiment (k) can be both a recombinant and chemically synthesized protein.

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Applicant respectfully requests reconsideration and withdrawal of this rejection as against amended claim 81 and the new claims for the following reason. In new independent claim 103 from which claim 81 depends, Applicant has eliminated the terms "analog", "homologs" and "fusion proteins". The claims use the phrase "an amino acid sequence that differs from a sequence of (a) through (f) by up to four codon changes in the nucleic acid sequence encoding the amino acid sequence." Support for fragments of these sequences is contained in the specification as stated above. These amendments are supported at page 16, lines 4-8 and line 25 through page 17, line 8. See, also, the Rule 132 Declaration for further support of the activity of the protein and peptide fragments of this invention.

Reconsideration and withdrawal of this rejection against all pending claims is requested.

(c) The Examiner has rejected claim 102 and has asserted that the same omits steps.

Applicant respectfully requests reconsideration and withdrawal of this rejection for the following reason. Cancellation of claim 102 renders this rejection moot.

Withdrawal of this rejection is requested.

35 USC § 102 Rejection

Claims 10-13, 39, 67, 81, 83, 100, and 102 are rejected under 35 USC § 102(b) over Zhang et al., *Cell*, **89**:275-285 (April, 1997).

The Examiner has asserted that Zhang teaches the claimed invention by teaching proteins comprising fragments of SEQ ID NO:2 and SEQ ID NO:14, recombinant production of the proteins, immunizing animals with the proteins, detection of antibodies which bind to the proteins, and fusion proteins of the proteins.

Applicant respectfully requests reconsideration and withdrawal of this rejection in view of the above-noted amendments, the attached Declaration under Rule 131 and the following remarks.

In the attached Declaration under Rule 131, the inventor provides evidence of conception of the claimed invention from a time prior to at least April 18, 1997, the publication date of Zhang. Specifically, the evidence attached to the Declaration, as well as the priority application, i.e., US Provisional Patent Application No. 60/051,271 ('271), demonstrates that the inventor had possession of the P7-1 clone, i.e., the nucleic sequence of SEQ ID NO: 1, and the corresponding amino acid sequence of SEQ ID NO:2. In the present application, these same sequences are disclosed as SEQ ID NOS: 1 (nucleic acid) and 2 (corresponding amino acid) and 13 (nucleic acid) and 14 (corresponding amino acid). Because the attached Declaration attests to conception of the P7-1 clone by the inventor before April 18, 1997, Zhang is thus disqualified as a prior art reference against claims directed to the same.

With regard to the peptides encoded by SEQ ID NOS: 3, 7 and 11 of the present claims, Zhang does not disclose or suggest this component of the invention. Zhang refers to an analysis of the VlsE of *B. burgdorferi*, strain B31, including its cassette strings. Zhang discusses the recombination of the sequences and refers to the sequence variation as a mechanism of maintaining surface protein function. Zhang does not disclose any sequences in the VlsE of strain B31 as isolated peptides or fragments thereof. Nor does Zhang mention any use of such peptides for diagnostic or other purposes. Zhang thus cannot be held to suggest any of the peptides claimed by inventors as encoded by SEQ ID NOS: 3, 7 and 11 or fragments thereof. Therefore, the claims directed to such sequences and fragments thereof are free of this prior art.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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Appendix A

Version with Markings to Show Changes Made

In the Specification

Amendment to page 2:

Publications relating to proteins and polypeptides of *Borrelia burgdorferi* have suggested their use as diagnostic or pharmaceutical agents. Such proteins and polypeptides include outer surface proteins A and B (OspA and OspB), flagellin, and other proteins designated P21, P39, P66, and P83 according to their estimated molecular weights [A. G. Barbour *et al*, Infect. Immun., 45:94-100 (1984); W. J. Simpson *et al*, J. Clin. Microbiol., 28:1329-1337 (1990); K. Hansen *et al*, Infect. Immun., 56:2047-2053 (1988); K. Hansen *et al*, Infect. J. Clin. Microbiol., 26:338-346 (1988); B. Wilske *et al*, Zentral. Bakteriol. Parasitenkd. Infektionshkr. Hyg. Abt. 1 Orig. Reihe. A., 263:92-102 (1986); D. W. Dorward *et al*, J. Clin. Microbiol., 29:1162-1170 (1991); published NTIS US patent application No. 485,551; European patent application No. 465,204, published January 8, 1992; International Patent Application No. PCT/US91/01500, published September 19, 1991; International Patent Application No. PCT/EP90/02282, published July 11, 1991; International Patent Application No. PCT/DK89/00248, published May 3, 1990; International patent application No. WO92/00055, published January 9, 1992].

Amendment to page 7:

Fig. 2 is a schematic depiction of portions of the DNA sequence of the novel P39.5 encoding a single open reading frame which encodes a deduced protein of 37.7 kDa. This DNA fragment is named 7-1, and the deduced protein referred to as P7-1. The region in black is a unique region spanning about bp769 to about bp854 of SEQ ID NO: 1. The region labeled IA spans about bp 1 to about bp 309 of SEQ ID NO: 1; IB spans about bp 855 to about bp 1189 of SEQ ID NO: 1[)]. Regions IA and IB have a 70% identity. Regions IIA, which spans about bp 310 to about bp494 of SEQ ID NO: 1 and IIB, which spans about bp 595 to about bp 769 of SEQ ID NO: 1, have

a 91% identity. Regions A, which spans about bp 208 to about bp 309 of SEQ ID NO: 1, and B, which spans about bp 495 to about bp 595 of SEQ ID NO: 1, have an 84% identity. Regions B and C, which together span about bp 1090 to about bp1189 of SEQ ID NO: 1, have a 90% identity.

Amendment to page 8:

Fig. 6 is a Western blot of lysates from spirochetes of *B.* [*bergdorferi*] *burgdorferi* strains JD1 and B31, and *B. garinii* strain IP90 developed with serum from monkeys needle-inoculated (lanes 1) and tick-inoculated (lanes 2) with the JD1 spirochetes, and antibodies from the latter serum affinity purified off of whole live JD1 spirochetes (lanes 3).

Amendments to page 10:

The gene fragment, designated 7-1, from *Borrelia garinii* strain IP90 inserted in pBluescript II plasmid was transformed in *E. coli* and deposited with the American Type Culture Collection, [12301 Parklawn Drive] 10801 University Boulevard, [Rockville] Manassas, [Maryland] Virginia ("ATCC") on June 27, 1997 under Accession No. 98478. When this gene fragment is expressed in *E. coli*, isolated as a pure protein and the protein used as an immunogen in mice, the antibody thus produced reacts with P39.5 of IP90. Other gene fragments, designated, 1-1, 3-1, 6-1, 9-1 and 12-1, from *Borrelia garinii* strain IP90 were similarly each inserted in pBluescript II plasmids, transformed in *E. coli* and deposited. These latter deposits were made with the ATCC on June 10, 1998 under Accession Nos. [_____] 98768 for 1-1, [_____] 98769 for 3-1, [_____] 98770 for 6-1, [_____] 98771 for 9-1 and [_____] 98772 for 12-1. All deposits were all made to meet the requirements of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure, and fully comply with the requirements of the United States Patent and Trademark Office for deposits for patent purposes. Sequences useful in the present invention may be obtained from these deposits.

Amendments to pages 18-19:

The P39.5 protein of the present invention, or fragments of it, as well as the vls-like cassette string proteins or fragments thereof, may also be constructed, using conventional genetic engineering techniques as part of a larger and/or multimeric protein or protein compositions. Antigens of this invention may be in combination with *B. burgdorferi* outer surface proteins, such as OspA and OspB, or various fragments of the antigens described herein may be in combination with each other. In such a combination, the antigen may be in the form of a fusion protein. The antigen of the invention may be optionally fused to a selected polypeptide or protein, e.g. *Borrelia* antigens OspA and OspB, other *Borrelia* antigens, and proteins or polypeptides derived from other microorganisms. For example, an antigen or polypeptide of this invention may be fused at its N-terminus or C-terminus to OspA polypeptide, or OspB polypeptide or to a non-OspA non-OspB polypeptide or combinations thereof. OspA and OspB polypeptides which may be useful for this purpose include polypeptides identified by the prior art [see, e.g. PCT/US91/04056] and variants thereof. Non-OspA, non-OspB polypeptides which may be useful for this purpose include polypeptides of the invention and those identified by the prior art, including, the *B. burgdorferi*, flagella-associated protein and fragments thereof, other *B. burgdorferi* proteins and fragments thereof, and non-*B. burgdorferi* proteins and fragments thereof.

Amendment to page 20:

A protein composition which may be a preferred alternative to the fusion proteins described above is a cocktail (i.e., a simple mixture) containing different P39.5 proteins or fragments, or different mixtures of the cassette string proteins of this invention. Such mixtures of these proteins or antigenic fragments thereof are likely to be useful in the generation of desired antibodies to *B. garinii.*

Amendment to page 24:

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Thus, an antibody of the invention is isolated by affinity purifying antiserum generated during an infection of a vertebrate animal, e.g., a rhesus monkey, with JD1 spirochetes, using as immunoabsorbant the native P39.5 antigen of IP90, or one or more of the cassette string proteins identified herein. Similarly, an antibody of the invention is isolated by immunizing mice with a purified, recombinant antigen of this invention, or a purified, isolated P39.5 of native origin. Monoclonal antibodies (MAbs) directed against P39.5 are also generated. Hybridoma cell lines expressing desirable MAbs are generated by well-known conventional techniques, e.g. Kohler and Milstein and the many known modifications thereof. Similarly desirable high titer antibodies are generated by applying known recombinant techniques to the monoclonal or polyclonal antibodies developed to these antigens [see, e.g., PCT Patent Application No. PCT/GB85/00392; British Patent Application Publication No. GB2188638A; Amit et al., Science, 233:747-753 (1986); Queen et al., Proc. Nat'l. Acad. Sci. USA, 86:10029-10033 (1989); PCT Patent [Application] Publication No. [PCT/]WO9007861; [and] Riechmann et al., Nature, 332:323-327 (1988); Huse et al, Science, 246:1275-1281 (1988)[a]].

Amendment to pages 24-25:

Alternatively, the antigens are assembled as multi-antigenic complexes [see, e.g., European Patent Application No. 0339695, published November 2, 1989] or as simple mixtures of antigenic proteins/peptides and employed to elicit high titer antibodies capable of binding the selected antigen(s) as it appears in the biological fluids of an infected animal or human.

Amendment to page 27:

In a similar embodiment, this diagnostic method involves detecting the presence of naturally occurring anti-P1-1, anti-P3-1, anti-P6-1, anti P7-1, anti-P9-1, and/or anti-P12-1 antibodies which are produced by the infected human or animal patient's immune system in its biological fluids, and which are capable of binding to the antigens of this invention or combinations thereof. This method comprises the steps of incubating [a]

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one or preferably, a mixture, of these antigen(s) of this invention with a sample of biological fluids from the patient. Antibodies present in the fluids as a result of *B. burgdorferi* infection will form antibody-antigen complexes with the antigen(s). Subsequently the reaction mixture is analyzed to determine the presence or absence of these antigen-antibody complexes. The step of analyzing the reaction mixture comprises contacting the reaction mixture with a labeled specific binding partner for the antibody.

Amendment to pages 38-39:

A Western blot (Fig. 6) was prepared of lysates from spirochetes of *B. burgdorferi* strains JD1 and B31 and *B. garinii* strain IP 90 developed with serum from monkeys needle-inoculated and tick-inoculated with the JD1 spirochetes, and antibodies from the latter serum affinity purified off of whole live JD1 spirochetes. The affinity purified antibody recognized four antigens on Western blots of whole lysates from spirochetes of *B. burgdorferi* JD1. The antigens were named P1 (Relative molecular mass (Mr) 39-40,000), P2 (Mr 35-37,000), P3 (Mr 22-24,000) and P4 (Mr 18-19,000). These antigens were also recognized, as expected, by serum samples from needle-inoculated animals and by serum from tick-inoculated monkeys. In addition, this Western blot indicated that the affinity-purified antibodies recognized what appeared to be P1, P2, and P4 on B31 spirochetes and what appeared to be P1 (but with a slightly higher relative molecular mass) in *B. garinii* as well as an additional antigen of higher relative molecular mass. These two latter antigens were also exclusively recognized by the sera from both needle- and tick-inoculated animals. P1 was eventually identified as P39, also known as BmpA. The similar antigen present on IP90 spirochetes was tentatively identified as P39.5 and was shown on the Western blot discussed above.

In the Claims

Cancel claims 10, 12, 13, 39, 67, 83, 100 and 102.

Amend claim 81 as follows.

81(Amended). A kit for diagnosing infection with [B. burgdorferi] *a causative agent of Lyme Disease* in a human or animal comprising a [P39.5] protein or [fragment thereof of claim 67] peptide of claim 103.

Add new claims 103 to 107 as follows:

103(New). A recombinant or synthetic protein or peptide that reacts with antibodies to the causative agent of Lyme Disease in infected humans or animals, said protein or peptide selected from the group consisting of:

(a) an amino acid sequence of SEQ ID NO. 2;

(b) an amino acid sequence of SEQ ID NO. 14;

(c) an amino acid sequence encoded by SEQ ID NO. 3;

(d) an amino acid sequence encoded by SEQ ID NO. 7;

(e) an amino acid sequence encoded by SEQ ID NO. 11;

(f) an amino acid sequence of a fragment of (a) through (e) of at least five amino acids in length; and

(g) an amino acid sequence that differs from a sequence of (a) through (f) by up to four codon changes in the nucleic acid sequence encoding the amino acid sequence.

104(New). The protein or peptide according to claim 103, wherein said fragment is at least eight amino acids in length.

105(New). The protein or peptide according to claim 103, wherein said peptide or protein is coupled to a substrate that immobilizes said peptide or protein.

106(New) The protein or peptide according to claim 103, wherien said peptide or protein is coupled to a detectable label or signal generating reagent.

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107(New) The kit according to claim 81, further comprising at least one of the group consisting of a substrate that immobilizes said peptide or protein, a detectable label, a labeled conjugate, and a signal generating reagent.